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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/074,328	GROTELUESCHEN HALL ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11.19.2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *101, 104-106, 111-112 and 116-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *101,104-106,111,112 and 116-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/19/2008 has been entered.

2. Currently, claims 101, 104-106, 111-112 and 116-125 are pending in the instant office action. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. This action is Non-FINAL.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The rejection under 35 USC 102(b) as anticipated by Dahlberg, made in the previous office action is withdrawn in view of the amendment to claim 101. Dahlberg does not teach a nucleic acid structure which meets the limitations now required in sections b, c and d of claim 101.

5. The rejection under Obviousness type double patenting over application claims 1-7 of application 11/031,487 is withdrawn in view of the cancellation of those claims.

Claim Rejections - 35 USC § 103

6. Claims 101, 104-106, 111-112, 116-117, and 123-125 rejected under 35 U.S.C. 103(a) as being unpatentable over Dahlberg in view of Harrington II (JBC, vol 270, pages 4503-4508, 1995).

With regard to claim 101, Dahlberg teaches a set of reagents that comprises a 5' nuclease lacking synthetic activity wherein the 5' nuclease functions to cleave a nucleic acid cleavage structure at a temperature of at least 55 deg C (see example 2). Dahlberg further teaches a target nucleic acid which contains a second region which is downstream and contiguous to a first region (see Fig. 16b, pilot oligonucleotide). Dahlberg teaches a first oligonucleotide containing a charged adduct (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group) and a second oligonucleotide that form an invasive cleavage structure in methods of detecting specific target nucleic acid sequences. However, Dahlberg does not teach a first oligonucleotide which comprises a portion completely complementary to the entire length of said first region of said target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion, said 5' portion completely complementary to the entire length of said second region of said target.

With regard to claim 104, Dahlberg teaches administering the oligonucleotide target complex to a gel, which is considered a solid support.

With regard to claims 105 and 106, Dahlberg teaches a method wherein cleavage structures are subjected to cleavage reactions with 5' nucleases wherein oligonucleotides of the cleavage structure are attached to solid supports (see pages 11-12, figure 23), whereby cleavage structures are released from the immobilized structure for further analysis.

With regard to claim 112, Dahlberg teaches a buffer solution.

With regard to claim 116, the claim sets forth no structural limitations for "linker". Therefore the term has been given its broadest reasonable meaning which encompasses the sugar group of the nucleotide.

With regard to claim 101, Harrington II teaches nucleic acid cleavage structures (double flap #1 and #2, figure 5) where the target (AI4) comprises a first region and a second region wherein the second region is contiguous to and downstream of said first region, a first oligonucleotide (HJ46) which comprises a charged adduct (a "charged adduct" is broadly interpreted to encompass a single nucleotide or charged phosphate group) and a portion completely complementary to the entire length of said first region of said target nucleic acid, and a second oligonucleotide comprising a 3' portion and a 5' portion (double flap #1: HJ77, double flap #2:HJ78), said 5' portion completely complementary to the entire length of said second region of said target. With regard to claims 124 and 125, the first oligonucleotide comprises an uncleavable region) Harrington II further teaches that the double flap structures were cleaved more efficiently by FEN-1, a 5' nuclease lacking synthetic activity which functions to cleave a nucleic acid cleavage structure (structures shown in figure 5A).

With regard to claim 117, any nucleotide or nucleic acid is detectable. Alternatively, the first oligonucleotide taught by Harrington II comprises a label at its 5' end (claim 123).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the target detection method of Dahlberg to include the double flap structure taught by Harrington II with a reasonable expectation of success. The ordinary artisan would have been motivated to use the flap structures taught by Harrington II in

the target detection method of Dahlberg because Harrington II teaches that the double flap structures were cleaved more efficiently by a 5' nuclease lacking synthetic activity which functions to cleave an invasive cleavage structure. Further, Harrington II teaches that FEN-1 is capable of cleaving a 5' flap endonucleolytically and has a double stranded specific 5'-3' exonuclease activity which is similar to exonuclease VI, the 5'-3' exonuclease domain of E coli DNA polymerase I and identical to activity necessary for in vitro DNA replication by mammalian cell extracts.

7. Claims 118-119 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahlberg and Harrington II, as applied to claims 101, 104-106, 111-112, 116-117, and 123-125, further in view of Urdea.

The teachings of Dahlberg and Harrington II are set forth above.

Dahlberg and Harrington II do not teach wherein the first oligonucleotide comprising a charged adduct comprises a detectable molecule which is flourescein (claims 118-119) or wherein the charged adduct comprises at least one amino modified base (claim 122), however Urdea teaches detection of cleaved labeled nucleic acid molecules attaches to a solid support wherein separation of the label from the solid support is detected and indicates cleavage (col. 8, lines 47-55, Figures 2 and 3). Urdea further teaches labeling the nucleic acid with fluorescein which is incorporated on an amino modified base such as cytosine or uracil (col. 9, lines 45-50). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to label the first oligonucleotide of Dahlberg and Harrington II with fluorescein on an amino modified base, as taught by Urdea because Urdea teaches detection of

cleaved nucleic acids and teaches labels such as fluorescein on an amino modified base can be used. The ordinary artisan would have been motivated to improve the method of Dahlberg and Harrington II with the use of the labeled nucleic acid as taught by Urdea for ease of detection as taught by Urdea and to minimize the use of radioactively labels.

8. Claims 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahlberg and Harrington II, as applied to claims 101, 104-106, 111-112, 116-117, and 123-125, further in view of Corey.

The teachings of Dahlberg and Harrington II are set forth above. Dahlberg and Harrington II do not teach wherein the first oligonucleotide comprises a charged adduct which comprises at least one amino acid (claim 120), wherein the amino acid is lysine, arginine, aspartate, or glutamate (claim 121), however Corey teaches that the addition of positively charged peptides in a nucleic acid sequence accelerates and enhances hybridization of that nucleic acid sequence, and that peptides containing as few as four lysines increased Ka by 5 fold. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the assays of Dahlberg and Harrington II with the use of positively charged peptides taught by Corey in the oligonucleotide structures of Dahlberg and Harrington II, including the first oligonucleotide. The ordinary artisan would have been motivated to modify the oligonucleotides of Dahlberg and Harrington II for the purpose of accelerating hybridization, as taught by Corey, in the assays of Dahlberg and Harrington II, and thus enhancing the assays of Dahlberg and Harrington II.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 101, 104-106, 111-112, 116-120 and 122-125 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 12/346,322. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to the entire length of a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to the entire length of a second region of the target, wherein the second region is downstream of and contiguous to the first region of the target. Claims 1-7 of the '487 application are drawn to a kit comprising an invasive detection cleavage assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the 5' UTR of HCV (target) and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the HCV 5' UTR and it's 3' portion does not. As defined by

the specification of the '487 application, the 2nd oligonucleotide hybridizes to the target downstream of the first oligonucleotide, and a kit comprising "an invasive cleavage detection assay" encompasses a thermostable 5' nuclease (eg: FEN-1), wherein either the 1st or 2nd oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Accordingly, the claims of the '487 application and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claim 121 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 12/346,322 in view of Corey. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to the entire length of a first region of a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to the entire length of a second region of the target, wherein the second region is downstream of and contiguous to the first region of the target. Claims 1-7 of the '487 application are drawn to a kit comprising an invasive detection cleavage assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the 5' UTR of HCV (target) and a second oligonucleotide which

comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the HCV 5' UTR and it's 3' portion does not. As defined by the specification of the '487 application, the 2nd oligonucleotide hybridizes to the target downstream of the first oligonucleotide, and a kit comprising "an invasive cleavage detection assay" encompasses a thermostable 5' nuclease (eg: FEN-1), wherein either the 1st or 2nd oligonucleotide is attached to a solid support, a buffer solution, a third oligonucleotide complementary to a third region of the target upstream of the first region, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Although the claims of the '487 application do not teach a charged peptide which is lysine, arginine, aspartate, or glutamate, Corey teaches peptide-nucleotide adducts comprising lysine. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the use of lysine in the kit of the '487 application because Corey teaches the use of lysine in peptide-nucleotide adducts, as taught by the claims of the '487 application.

This is a provisional obviousness-type double patenting rejection.

12. Claims 101, 104-106, 111-112, 116-120, and 122-125 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 24-29 of copending Application No. 10/754,408. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first oligonucleotide comprising a charged adduct and a portion completely complementary to the entire length of the first region of a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5'

portion wherein the 5' portion is completely complementary to the entire length of the second region of the target, wherein the second region is downstream of and contiguous to the first region of the target. Claims 1-13 and 24-29 of the '408 application are drawn to a kit comprising oligonucleotides for a non-amplified oligonucleotide detection assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the a target containing a connexin 26 allele and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the target containing the connexin 26 allele and it's 3' portion does not. As defined by the specification of the '408 application, the 2nd oligonucleotide hybridizes to the target downstream of the first oligonucleotide, a non-amplified oligonucleotide detection assay comprises a thermostable 5' nuclease (eg: FEN-1), wherein either the 1st or 2nd oligonucleotide is attached to a solid support, a buffer solution, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Accordingly, the claims of the '408 application and the claims of the instant application are coextensive in scope and not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claim 121 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 24-29 of copending Application No. 10/754,408 in view of Corey. The claims of the instant application are drawn to a set of reagents comprising a thermostable 5' nuclease lacking synthetic activity, a first

oligonucleotide comprising a charged adduct and a portion completely complementary to the entire length of the first region of a target nucleic acid and a second oligonucleotide comprising a 3' portion and a 5' portion wherein the 5' portion is completely complementary to the entire length of the second region of the target downstream of and contiguous to the first region of the target. Claims 1-13 and 24-29 of the '408 application are drawn to a kit comprising oligonucleotides for a non-amplified oligonucleotide detection assay which comprises a first oligonucleotide comprising a 5' portion and a 3' portion which hybridizes to the a target containing a connexin 26 allele and a second oligonucleotide which comprises a 5' portion and a 3' portion wherein the 5' portion hybridizes to the target containing the connexin 26 allele and it's 3' portion does not. As defined by the specification of the '408 application, the 2nd oligonucleotide hybridizes to the target downstream of the first oligonucleotide, a non-amplified oligonucleotide detection assay comprises a thermostable 5' nuclease (eg: FEN-1), wherein either the 1st or 2nd oligonucleotide is attached to a solid support, a buffer solution, a charged label which is detectable, including a linker, a detectable molecule, an peptide, an amino modified base and an uncleavable region. Although the claims of the '408 application do not teach a charged peptide which is lysine, arginine, aspartate, or glutamate, Corey teaches peptide-nucleotide adducts comprising lysine. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the use of lysine in the kit of the '408 application because Corey teaches the use of lysine in peptide-nucleotide adducts, as taught by the claims of the '408 application

This is a provisional obviousness-type double patenting rejection.

14. The response provides no arguments with regard to the obviousness type double patenting rejections set forth above. Accordingly, the rejections are maintained for the reasons made of record above and in previous office actions.

Conclusion

15. No claims are allowable over the cited prior art.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday, Tuesday and Thursday from 9:00 AM to 3:00 PM.

NOTE: The examiner will be on Maternity Leave through August 2009.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Jehanne Sitton/

Primary Examiner
Art Unit 1634